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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/721,693	KAEMMERER, WILLIAM F.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-89* is/are pending in the application.

4a) Of the above claim(s) *2-4,6-8,11-13,15-18,20-23 and 26-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5, 9, 10, 14, 19, 24, 25, and 85-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Exhibit A: NCBI Online Printout of SCA1 .

DETAILED ACTION

Status of Application

Applicant's response filed July 6, 2006, has been considered. Rejections and/or objections not reiterated from the previous Office Action mailed on March 6, 2006, are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Amendments

Applicant's amendments to the claims are acknowledged. The amendments have been entered in full.

With the amendment of 3/6/06, Claims 1-89 are pending. Claims 2-4, 6-8, 11-13, 15-18, 20-23, and 26-84 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions and/or species, there being no allowable generic or linking claim.

Claims 1, 5, 9, 10, 14, 19, 24, 25, and 85-89 are currently under examination.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e)

has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submissions filed on July 6, 2006, have been entered.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, U.S. Provisional application 60/429,387, upon which benefit is claimed fails to provide adequate support under 35 U.S.C. 112 for claims drawn to medical systems comprising small interfering RNA, Claims 1, 5, 9, 10, 14, 19, 24, 25, and 85–89. The instant application clearly defines small interfering RNA (pages 14-15) as "double stranded RNA agents" that are "used to trigger RNA interference." As ordinarily used in the art, "small interfering RNA" normally refers to double stranded RNAs, which operate by a different biochemical pathway than ribozymes and antisense (single stranded) RNAs. Thus, antisense, ribozymes, and small interfering RNA are considered to represent distinct molecular agents. The earliest filed priority document in which adequate support is provided for medical systems comprising small interfering RNA is U.S. Provisional application 60/444, 614, filed 2/3/03. If applicant believes that support for the instant claims, drawn to medical systems comprising small interfering RNA agents, is present in the earlier filed priority document, applicant must, in responding to this Action, point out with particularity, where such support may be found.

Applicant's response to the issue of priority, in the remarks filed on 7/6/06, is acknowledged.

Claim Objections

Claims 1, 19 and 88 are objected to because of grammatical informalities.

Claim 88, as now written, is grammatically awkward. The claim recites "wherein said small interfering RNA is of having a length." Furthermore, the claim lacks parallelism with regard to the use of "having" and "comprises" to describe the siRNA. It is suggested that the claim be amended to remove "is of" and to use "has" together with "comprises."

Appropriate correction is required.

Claim 19 recites "ataxin1," whereas all other pending claims recite "ataxin-1" with a hyphen. For consistency and clarity, applicants are requested to use a single spelling and/or nomenclature for each limitation in the claims.

As amended, Claim 1 is confusing. In part d, the claim now recites a delivery means for delivering siRNA from said intracranial access device through a stereotactically implanted catheter. It is unclear how the stereotactically implanted catheter is related to or connected to the delivery means. It appears as though Applicant intended to mean that the stereotactically implanted catheter is the delivery means, however, the claim does not accurately reflect that. Claim 9 renders the claim further unclear because it recites wherein the access device is a catheter. Thus, the embodiment of claim 9 appears to comprise two catheters. How are these catheters connected or arranged? It is unclear. Also unclear in light of the amendment to claim 1 is the embodiment of claim 24, which now claims a system comprising an external syringe in an intracranial access port, along with a stereotactically implanted catheter, and a delivery means.

Clarification or correction is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 89 recites the limitation "the ataxin-1" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Applicants did not specifically address the rejection of claim 89 for lack of antecedent basis in their reply.

In addition, Claim 89 recites a "small interfering RNA that is able to stably interact with the ataxin-1 mRNA. It is unclear what is meant by "stably interact." The term " stably interact" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Applicants argue that the instant application, specifically paragraph 60, discloses the meaning of the phrase "stably interact." A review of paragraph 60, which appears on pages 14 to 15 of the specification as filed, shows that stably interact is defined as an interaction of the small interfering RNA with target nucleic acid (e.g., by forming hydrogen bonds). However, "stably' is a relative term that modifies interact, and the instant specification fails to adequately explain by way of exemplary structures or by measurable criteria, such as binding energies or minimum number of base-paired nucleotides, what structures fall within the scope of the limitation "stably interact."

Accordingly, the rejection for indefiniteness is maintained.

Appropriate correction is required.

Claim 1 recites "said patient." There is insufficient antecedent basis for this limitation in the claim.

***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 9, 10, 14, 19, 24, 25, and 85-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, complete or partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

The claims are drawn to a medical system for treating a neurodegenerative disorder in a human, comprising an intracranial access device, a mapping means for locating a predetermined location in the brain, a deliverable amount of siRNA capable of inhibiting expression of the gene responsible for the neurodegenerative disorder, and a means for delivering the siRNA to the location in the brain of the patient.

Dependent claim 5 limits the invention to a system for treating spinocerebellar ataxia type 1. Dependent claim 19 limits the invention to one comprising siRNA specific for the SCA1 gene.

The claim limitation "a mapping means for locating a predetermined location in the brain of a patient," recited in claim 1, the base claim, is being treated under 35 U.S.C. 112, sixth paragraph, as a means for performing a specified function, and that the limitation shall be construed to cover the corresponding structure or material described in the specification and equivalents thereof.

The claims are extremely broad. For example, in their broadest embodiments the claims include medical systems for treating any neurodegenerative disorder in human.

The instant rejection is two-fold: 1) Adequate written description does not exist in the instant application for the genus of small interfering RNAs capable of inhibiting the expression of all genes responsible all neurodegenerative disorders, or even all genes responsible for spinocerebellar ataxia type 1; 2) Adequate written description does not exist in the instant application for a mapping means for locating a predetermined location in the brain of a patient.

The specification does not adequately allow persons of ordinary skill in the art to recognize that applicant(s) were in possession of the entire genus of medical systems as now claimed in the instant claims.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed (pg. 1117). Because the level of skill and knowledge in the art increases over time, it is essential to determine possession as of the effective filing date.

A disclosure in a parent application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement; the disclosure must describe the claimed invention with all its limitations." (Tronzo v. Biomet Inc., 156 F.3d 1154, 1158, 47 USPQ2d 1829, 1832 [Fed. Cir. 1998]). The specification need not, however, describe the claimed invention using the same words as the claims (Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 [Fed. Cir. 2000]).

In the instant case, the specification does not enable the skilled artisan to clearly envision the distinguishing characteristics or features of the encompassed genus of small interfering RNAs (siRNAs) that inhibit genes responsible for all neurodegenerative disorders.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

MPEP 2163 states in part that "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. >The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004).

In the instant case, applicants have not satisfied either of these criteria. That is, the instant application describes neither a representative number of species nor any feature common to the genus of siRNAs that inhibit the expression of genes responsible for neurodegenerative disorders such that one of skill in the art would recognize that Applicants were in possession of the entire genus at the time of filing.

While the specification adequately describes three (3) siRNAs at pages 30 and 31 that are said to inhibit human ataxin-1 mRNA in cell culture, by fully setting forth their structures and functions, and by describing the materials and methods needed to make and use such agents, adequate written description does not exist for the virtually unlimited number of other siRNAs in the claimed genus. Thus, applicants have not shown possession of the claimed medical systems comprising a delivarable amount of said siRNAs.

MPEP §2163 states, in part: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)."

In the instant case, the prior art indicates a degree of unpredictability in the art as it relates to siRNA structure and function.

For example, Holen et al. (2002) *Nucleic Acids Res.* 30:1757–1766 tested several siRNAs corresponding to different target sequences in human coagulation trigger tissue factor (hTF) for their ability to induce silencing of the hTF gene. Of the several siRNAs synthesized and tested only a few produced significant reduction in expression of hTF, suggesting that accessible siRNA target sites may be rare in some human mRNAs. Moreover, siRNAs targeting different sites in hTF demonstrated dramatic differences in silencing potency. Although strong positional effects were observed and regions of high GC content seem to be targeted less efficiently than

those of low GC content, Holen et al. concluded that the factors determining the differences in siRNA efficiency remain unclear and that susceptible RNAi target sites in some human genes may be rare.

The results of Holen et al. suggest that it is difficult to predict a priori what sequences to target in a gene with siRNAs to induce efficient silencing by RNAi. In addition, there is growing body of evidence suggesting that specific siRNAs may produce unwanted and unanticipated off-target effects (see Jackson et al. 2003, *Nature Biotechnology* 21:635-637). Their results indicate that treating cells with different siRNAs targeting different sequences in the same RNA transcript may result in different but reproducible off-target effects.

Accordingly, the art indicates that researchers must empirically determine which sequences and their corresponding siRNAs work best for RNAi-mediated gene silencing.

Thus, the prior art indicates a fair degree of variability in the genus of siRNAs required for the claimed invention. Applicants have not shown that they were in possession of the entire genus of the siRNAs now claimed.

A critical element of the lack of written description of the genus of siRNAs capable of inhibiting genes responsible for all neurodegenerative disorders is the lack of written description of the genus of targets—the genes responsible for all neurogenerative disorders. While Applicants describe a number of different gene targets, claims 16-22, for example, applicants do not describe a representative number of genes, or a common feature of the genus of genes, responsible for all neurodegenerative diseases. Logically, without a description of the target sequences, applicants cannot describe the siRNAs needed to target those sequences.

Accordingly, only medical systems comprising the use of the structurally and functionally defined siRNAs described in the specification, including those recited in claim 88, meet the written description requirement.

With regard to the second part of this rejection, adequate written description does not exist in the instant application for a mapping means for locating a predetermined location in the brain of a patient.

A means- (or step-) plus-function claim limitation is adequately described under 35 U.S.C. 112, para. 1, if: (1) The written description adequately links or associates adequately described particular structure, material, or acts to the function recited in a means- (or step-) plus-function claim limitation; or (2) it is clear based on the facts of the application that one skilled in the art would have known what structure, material, or acts perform the function recited in a means- (or step-) plus-function limitation.

In the instant case neither of these criteria is satisfied. A review of the instant application fails to find any description of a "mapping means for locating a predetermined location in the brain of patient."

Consequently, the Examiner has applied broadest reasonable interpretation to include such means as stereotactic atlases and anatomical atlases, including those based on magnetic resonance imaging (see rejection below).

In response, Applicant argues that atlases such as those applied by the Examiner are inadequate to meet the requirements of the claimed invention, or would not be sufficient to allow one of skill in the art to perform the delicate task of delivering siRNA to a predetermined location in the brain (see Applicant's remarks of 1/5/06, page 12, and 3/6/06, page 13). In short,

Applicant argues that anatomical atlases and even detailed stereotactic atlases are not "mapping means" within the scope of the invention.

In the remarks, Applicant argues that mapping means is coordinates of Paxinos and Cahill. Applicants mapping means is related to precise live coordinates and structures in a patient that are generated for each individual brain (Applicant's remarks of 1/5/06, page 12).

However, the particular structure or characteristics of this mapping means remain unclear, as the instant application fails to describe any mapping means.

In particular, Applicants argue that an anatomical map, such as that provided by Paxinos et al., is a useful teaching tool in gross anatomy, but is inadequate for mapping live brains.

> "Placing a delivery device into the live brain of a patient requires exquisite preciseness that can not be obtained from just looking at the maps and coordinates of Paxinos and Cahill. Applicants mapping means is related to precise live coordinates and structures in a patient that are generated for each individual brain. As you may know, there is an infinite variation of head sizes, shapes, and brain anatomy. Applicant's mapping means is tied to live mapping systems of a patient's brain." (Applicants' Remarks, pp. 6-7)

With regard to Applicants' assertion that the Paxinos et al. and Cahill et al. references are insufficient for use in the claimed invention as a whole, the Examiner reminds Applicants that broadest reasonable interpretation of "mapping means for locating a predetermined location in the brain of a patient," according 35 USC §112, sixth paragraph, includes the corresponding structure described in the specification and equivalents thereof." (See MPEP §2181, Section II, for example).

A review of the instant application fails to find any disclosure clearly describing the corresponding structures, apparatus, or devices intended by Applicants to be used as a "means for mapping a predetermined location in the brain of a patient" in the claimed invention. Thus, no guidance is given as to what does or does not constitute a "means for mapping." Therefore,

the Examiner must interpret the recitation to include any technically feasible, practical means for locating a predetermined location in the brain of a patient.

It is quite clear that the references cited below (Paxinos et al., Serra et al., and Clark et al.) are designed to be used in conjunction with stereotactic frames, mounted on the heads patients for delicate neurosurgical methods, and that one of skill in the art would know that allowances and/or adjustments in the coordinates may be necessary depending on the age of the animal being used. Furthermore, the instant claim does not specify or require any minimum degree of precision that must be obtained with the recited "mapping means." It is sufficient that the mapping means would enable the researcher to target any structure or general region in the brain: the forebrain or hindbrain, for example.

Nothing in the claims or the specification excludes the use of an anatomical atlas or stereotactic frame and it is clear that stereotaxic coordinates, such as those provided by Paxinos et al. and others in the art, cited below, are routinely used by researchers to implant devices and delivery reagents into the brains of mice and humans for investigational and therapeutic purposes.

For instance, the instant application (page 28), under "Devices," states "Delivery occurs through a stereotactically implanted polyurethane catheter." Whitesell et al. state that rats with stereotactically implanted catheters were used for their experiments (page 4666). Dorri et al. (1997) *Exp. Neurology* 147:48-54, who teach a system for injecting antisense oligonucleotides combined with a fluorescent dye into the hippocampus of rats for alteration of neural activity, state that "A guide cannula was inserted into the left hippocampus using coordinates given in Paxinos and Watson ... adjusted for the young age of the animals (1.8 mm lateral, 4.16 mm

posterior, 2.7 mm ventral) (page 49). Zhang et al. (1996) *J. Mol. Neuroscience* 7:13-28, who teach a system for injecting FITC-labeled antisense oligonucleotides into the lateral cerebral ventricles of mice, state that "Mice were anesthetized with halothane and the phosphorothioate dopamine receptor antisense oligonucleotide labeled with FITC ...was injected stereotactically into the lateral cerebral ventricle using a plastic mold ..." (page 14) Thus, it is clear that many researchers in the field of brain research have relied on Paxinos et al. or similar stereotaxic atlases as references to deliver materials to specific locations in the brains of mice and rats.

If, as Applicants assert, anatomical atlases, which give precise 3-D stereotaxic coordinates of brain structures, are not within the scope of the recitation "means for mapping," and such atlases are unsuitable for use in the claimed invention, what is within the scope of the recitation? What does a "means for mapping" consist of? What is it? What does it look like? Would one of skill in the art know what does or does not fall within the scope of the recitation "means for mapping"? The specification gives neither general guidance nor specific examples of any structure clearly informing one of skill in the art what does or does not constitute "a mapping means for locating a predetermined location in the brain of a patient."

Accordingly, the instant claims are rejected for lack of written description.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Double Patenting

Claims 1, 9, 10, 14, 19, and 25 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 8, 16, 17, and 29 of copending Application No. 10/962,732 (US 2005/0048641) in view of Paxinos et al. (2001) *The Mouse Brain in Stereotaxic Coordinates.* Academic Press, 2nd Ed; and Cahill et al. (1995) *Atlas of Human Cross-sectional Anatomy*, Wiley-Liss, 3rd ed.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Copending application No. 10/962,732 and the instant application are both directed to a medical device, or system, for transfusing interfering RNA (siRNA) into tissues and cells in living organisms, including humans. Claim 1 of the instant application recites a medical system for treating a neurodegenerative disorder "in a patient," comprising an intracranial access device, a mapping means, a deliverable amount of siRNA or vector encoding siRNA, and a delivery means. Claims 9 and 10 limit claim 1 by stating that the access device is a catheter or access port. Claim 19 limits claim 1 by stating that the siRNA targets SCA1 mRNA. Claim 25 limits claim 1 by stating that the delivery means is an infusion pump.

Claims 7, 8, 16, 17, and 29 of copending Application No. 10/962,732 recite a similar system for delivering small interfering RNA targeted to a gene, SCA1, associated with a neurodegenerative disease. Claim 7, the base claim, recites a system comprising an implantable infusion pump, a reservoir, a fluid comprising an RNAi agent, and a catheter. The implantable infusion pump is defined as being either implantable or external, may have a port into which a

needle can be inserted to inject a therapeutic agent, and may further have a catheter, and a catheter port (paragraph 24) for delivering an RNAi agent to a specific location in the brain. Paragraph 29 describes a specific embodiment of the claimed system; namely, intraparenchymal and intracerebroventricular delivery devices (illustrated in Fig. 3) for delivering agents to the brain, and clearly embodies an access port and catheter. Thus, the device claimed by claims 7, 8, 16, 17, and 29 of copending Application No. 10/962,732 may serve to deliver siRNA intracranially to different regions of the brain and is, therefore, considered to encompass "medical systems" such as those claimed in the instant application.

Furthermore, Applicant states on page 28 of the instant application (10/721,693) that "The envisioned route of delivery is through the use of implanted, indwelling, intraparenchymal catheters that provide a means for injecting small volumes of fluid containing AAV or other vectors directly into local brain tissue." On page 29 of the instant application, Applicant states that "...the present invention includes the delivery of small interfering RNA vectors using an implantable pump and catheter, like that taught in U.S. Patent No. 5,735,814 and 6,042,579..."

Copending Application No. 10/962,732 does not claim a "mapping means" or means for locating a predetermined location in the brain. However, it would be obvious to one of skill in the art to combine the teachings of copending Application No. 10/962,732 with those of a standard anatomical atlas such as that of Cahill et al. or Paxinos et al., who provide not only an anatomical guide of the mouse brain but also stereotaxic coordinates for different brain locations. These anatomical atlases may serve as a means for mapping predetermined locations in the brain. A review of the List of Structures in the Paxinos et al. reference shows that several of the "predetermined locations" recited in claims 11-13 and 15 are described. These include, the

substantia nigra, the cerebral cortex, the hippocampus, the striatum (caudate putamen), the subthalamic nucleus, and the medial (fastigial) cerebellar nucleus. The Atlas of Human Anatomy, by Cahill et al., shows some of alternative recited structures; specifically, Cahill et al. teach the location of the dentate nucleus, enabling the skilled artisan to position the implantable infusion pump and catheter in a manner that would deliver the siRNA to the desired brain location.

Accordingly, one of skill in the art would conclude that the invention defined in the instantly claimed invention of this application (No. 10/852,997) is an obvious variation of the invention defined in copending Application No. 10/721,693 since each of the required elements are present and each of the devices or systems is clearly intended to serve as a system for delivering small interfering RNA (specifically siRNA targeting SCA1 mRNA) intracranially to treat a neurodegenerative disease.

Thus in the absence of evidence to the contrary, the instantly claimed invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Applicant's arguments

Applicant's request for postponement of rejection under this section is non-responsive. The rejection is maintained.

Claim Rejections - 35 USC § 103

Claims 1, 9, 10, 14, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al. (2002) *Nature* 20:1006–1010; Driscoll et al. (WO 01/49844); Cahill et al. (previously cited); Paxinos et al. (2001) *The Mouse Brain in Stereotaxic Coordinates.* Academic Press, 2nd Ed; Serra et al. (1996) *Medical Image Analysis* 1(4):317-329; Morel et al. (1997) *J. Comparative Neurology* 387:588-630; Clark et al. (1997) *J. Neuroscience* 17:7385-7395; and Salehi et al. (1999) *J. Neural Transm.* 106:955-986.

As amended, Claim 1 now recites a medical system for treating a neurodegenerative disorder in a human live patient, comprising an intracranial access device, a mapping means, a deliverable amount of siRNA capable of inhibiting expression of a gene responsible for the disorder, and a delivery means.

As a preliminary matter, Applicants are advised that the claim limitation "a mapping means for locating a predetermined location in the brain of a patient" is being treated under 35 U.S.C. 112, sixth paragraph, as a means for performing a specified function, and that the limitation shall be construed to cover the corresponding structure or material described in the specification and equivalents thereof.

As explained above, the instant application does not explicitly or implicitly describe any structure or material corresponding to the recited "mapping means." The Examiner is therefore giving the recitation its broadest reasonable interpretation. A mapping means for locating a predetermined location in the brain of a patient, including a human patient, may reasonably be construed to include an anatomical atlas, electronic or printed, especially those designed to assist with neurosurgery and neurosurgical implants.

Applicants are advised that the recitation "means for locating a predetermined location in the brain" may be achieved simply by the mental act of 1) choosing a brain structure that one wishes to locate, based on, for example, its documented association with a particular neurodegenerative disorder (i.e., predetermining); and 2) referring to an atlas to determine its relative location and position in the brain (mapping or locating).

Applicants are further reminded that the instant claim is not a method or process for performing gene therapy. The claim is drawn to an assembly or apparatus, comprising the four interrelated structures now recited in parts a-d of the claim.

While applicants have amended the preamble to recite "in a human live patient," part a continues to recite "a patient," and does not specifically refer to a human patient. Thus, the preamble is not considered to limit the invention to the treatment of humans alone but simply recites an intended use. In the instant case, the preamble does not appear to limit the structure of the claimed invention (MPEP §2112.02), and the body of the claim does not refer to back to the "human live patient" recitation in the preamble in a way that would breath life and meaning into the claim.

However, for purposes of this examination, prior art is relied upon showing that the claimed system for treating neurodegenerative disorders in humans and mice would have been obvious at the time the instant invention was made.

Xia et al. teach a method for intracranial delivery of a vector encoding a small interfering RNA (siRNA). Specifically, Xia et al. teach a method for silencing gene expression *in vivo* in the brain of a mouse using a recombinant adenovirus encoding small interfering RNA (page 1007).

In a pilot experiment (described on pp. 1007-8), Xia et al. used a virus encoding siRNA specific for green fluorescent protein (GFP) to silence eGFP expression in transgenic mice that express eGFP endogenously in their brain tissue. Xia et al. state that the recombinant virus was "injected" into the brain, specifically the brain striatal region (page 1007, 1010). Thus, Xia et al. delivered the vector directly to the brain by "injection." This is taken to mean that a delivery means, such as a syringe, was used to inject the siRNA-encoding vector into the brains of the mice subjects. The device is therefore considered to have functioned both as "an intracranial access device" and as "a delivery means," as recited in the instant claim. Xia et al. state that the virus also contained a dsRed expression cassette, which allowed for unequivocal localization of the injection site by fluorescence microscopy. Thus, "a mapping means" or means for mapping a "predetermined location in the brain" is also present in the Xia et al. system.

Xia et al. show that GFP expression was reduced in the injected hemisphere only (page 1007). Thus, Xia et al. teach a "system" for reducing gene expression in the brain using a vector encoding a small interfering RNA, specifically, a 21-bp hairpin RNA—i.e., a double stranded, interfering RNA—targeting eGFP (page 1009).

Xia et al. further state that their results support the idea that "hairpin RNA can reduce target gene expression through siRNA-mediated mechanisms." (page 1009, 1st column) and go on to suggest that "One powerful therapeutic application of siRNA would be to reduce expression of toxic gene products in dominantly inherited diseases such as polyglutamine (polyQ) neurodegenerative disorders." (page 1008, 2nd column) This suggests that one of skill could use siRNA encoding vectors *in vivo* to reduce endogenous gene expression in the brain, as shown by Xia et al. See also page 1009, 2nd column. Thus, Xia et al. clearly teach a system

within the scope of Claim 1 that is suitable for treating a neurodegenerative disease using small interfering RNA.

Xia et al., therefore, demonstrate that endogenously expressed genes can be silenced with siRNAs that are directly injected into the brain.

Driscoll et al. (cited in Applicant's IDS) teach methods for making and using vectors encoding short hairpin RNAs targeting genes associated with neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, and Parkinson's disease (pages 3-5; 41-46). Exemplary vectors are illustrated in Figs. 5 and 6. One vector in particular, expresses an inverted repeat sequence specific for alpha synuclein, a gene associated with Parkinson's gene. Figs. 1 and 2 outline the procedure and principles for preparing and using said shRNA expressing vectors to inhibit gene expression. The expressed RNAs are predicted to form hairpin RNAs, having double stranded structures that mediate gene-specific inhibition via an RNAi mechanism. The vectors are said to be useful in the treatment of diseases such as Alzheimer's to reduce plaque formation.

Xia et al. and Driscoll et al. do not teach how to specifically target predetermined locations in the brain of a mouse or a human.

However, one of skill in the art following the Xia et al. teachings would be expected to refer to an anatomical atlas such as that provided by Paxinos et al., who provide not only an anatomical guide of the mouse brain but also stereotaxic coordinates for different brain locations, which may serve as "mapping means," enabling the skilled artisan to locate predetermined locations in the brain. The Paxinos et al. atlas is considered to be representative of any number of atlases that the skilled artisan might consult to "predetermine" specific locations in the brain of a

mouse. A review of the List of Structures in the Paxinos et al. reference shows that several "predetermined locations" are described. These include, the substantia nigra, the cerebral cortex, the hippocampus, the striatum (caudate putamen), the subthalamic nucleus, and the medial (fastigial) cerebellar nucleus. The Atlas of Human Anatomy, by Cahill et al., shows some of alternative recited structures; specifically, Cahill et al. teach the location of the dentate nucleus, enabling the skilled artisan to position the implantable infusion pump and catheter in a manner that would deliver the siRNA to the desired brain location.

Furthermore, the prior art is replete with detailed anatomical atlases of the human brain illustrating and describing 3-dimensional coordinates and relative positions of virtually every neural center in the brain. A review of the prior art finds several representative examples designed specifically to assist researchers and clinicians with neurosurgical and therapeutic applications in the brain.

For example, Serra et al. teach a medical system, materials and methods for clinical neurosurgical treatment of brain conditions. Specifically, Serra et al. describe a surgical planning system for stereotactic frame neurosurgery. Stereotactic neurosurgery is said to date back to 1906 (page 317). Using Stereotactic neurosurgery dates from 1906. Using X-rays, surgeons have hand-computed the coordinates of target lesions and adjusted a stereotactic frame to guide the delivery of a penetrating instrument (e.g. a biopsy needle, electrode etc.) to the chosen target location. The stereotactic frame is movably, and precisely controllably, attached to a fixation device, rigidly screwed to the skull, in a position established with millimetre precision. Only a narrow hole is opened in the skull, and no sight path opened in the
Brain (page 317).

Serra et al. describe technological improvements for surgery in human brains, comprising the use of CT and MR imaging, and the incorporation of detailed stereotactic atlases compiled over the years into their system of hardware and software for planning and carrying out neurosurgery. For example, Serra et al. describe an "electronic brain atlas" for identifying brain targets (page 320). Serra et al. describe the use of their system to target brain structures with almost any art-recognized surgical instrument, including probes and delivery devices. Accordingly, Serra et al. provide a detailed blueprint and disclose devices and software, and refer to severaly print publications, describing, teaching, and showing the use of stereotactic atlases to identify and locate virtually any target in the human brain.

One of skill interested in a particular region of the human brain, may, in addition to referring to Serra et al., use the teachings of Morel et al., among others, who teach a detailed atlas of the human thalamus. Morel et al. teach that the thalamus is a major target for surgical treatment, given its prominence in cognitive functions and association with pathophysiological disorders (page 588). Morel et al. teach that computer tomography and magnetic resonance imaging-guided stereotaxy and preoperative microelectrode recordings for localization of targets has aided stereotactic neurosurgery. Morel et al. present a detailed map of the human thalamus, including several important subthalamic structures (page 589, and Appendix), and teach the importance of adapting such atlases to different brain sizes. Overall, Morel et al. and Serra et al. are considered to be representative of the state of the prior art regarding the level of skill and knowledge available to those in the field of neurology and neurosurgery. Together, Morel et al. and Serra et al. show that those of skill in the art interested in delivering siRNA to specific locations in the brain to inhibit a specific gene responsible for a neurodegenerative disorder, as

taught by Driscol et al. and/or Xia et al., would have a reasonable expectation of success in locating and targeting virtually any region in the brain.

One of skill in the art wishing to treat a neurodegenerative disorder using siRNA or vectors encoding siRNA, would be expected to consult the prior art for information describing the pathology of the neurodegenerative disorder and its localization in the central nervous system. Here again, the prior art is replete with information regarding the physiological effects of several known disorders, including Alzheimer's and Spinocerebellar ataxia, to name a few.

For example, Clark et al. teach that spinocerebellar ataxia type 1, or SCA1, is a neurological disorder that affects the Purkinje cells, particularly those in the cerebellar cortex. Clark et al. attribute the disorder to abnormal function of ataxin-1 protein, resulting from a polyglutamine expansion. Salehi et al. teach that Alzheimer's disease affects the nucleus basalis of Meynert, the CA1 area of the hippocampus, and the hypothalamic tubermammillary nucleus.

Thus, Clark et al. and Salehi et al. are representative of the level of skill and knowledge in the prior art regarding the correlation between neurodegenerative disorders and brain pathology.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Xia et al., Driscoll et al., Paxinos et al., Serra et al., Morel et al., Clark et al., and Salehi et al. for the reasons given above to design, produce, and apply siRNAs and/or vectors encoding RNAi-active, hairpin RNAs, to treat neurodegenerative disorders in the brains of mice and/or humans to either study the role of gene expression and function in the development and progression of the disease or to treat the disease.

One would have been motivated to create and use such vectors because Xia et al. expressly teach that such vectors work to reduce endogenous gene expression and because RNA interference is taught by Xia et al. and Driscoll et al. as having the potential to relieve symptoms associated with neurodegenerative disorders.

Finally, one would have a reasonable expectation of success given that both Xia et al. and Driscoll et al. expressly describe methods, and give actual examples, for constructing and using shRNA (small hairpin RNA) expressing vectors for purposes of inhibiting the expression of genes associated with neurodegenerative diseases. Further, one of skill in the art armed with such vectors would have a reasonable expectation of success in locating and targeting a predetermined location in the brain, given that the prior art is replete with anatomical atlases and stereotactic guides such as those of Paxinos et al., Serra et al., and Morel et al for identifying and targeting specific brain structures, and given that the prior art is replete with information teaching which structures are primarily affected by several different neurodegenerative diseases, as exemplified by Clark and Salehi.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Arguments considered:

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In the instant case, Applicants argue that Driscol et al. does not teach or suggest intracranial access devices, mapping means, or the combined use thereof to deliver siRNA.

Applicants argue that Paxinos et al. does not teach or suggest which brain structures to target for siRNA therapy of a neurodegenerative disorder.

Applicants argue that the references do not teach a stereotactically implanted catheter, or use thereof to deliver siRNA for the inhibition of endogenously expressed genes.

The Examiner respectfully submits that Applicant's arguments are addressed by the instant rejection.

A stereotactically implanted catheter may be a needle that is left in place for a short or long duration. Nothing in the instant claim or the specification limits the term "implanted" to a device left in place for a specified period of time. "Implanted" for purposes of this examination is any device inserted or embedded in the cranium, such as a needle, as used by Xia et al.

The references are not relied individually but as a whole for what they taught or fairly suggested to one of skill in the art at the time the invention was made. One may reasonably infer from the combined teachings that siRNA therapy of endogenously expressed genes in the brain via direct injection techniques could be carried out with a reasonable expectation of success at the time the instant invention was made, and that, further, it was possible to steretactically locate and target regions within the brain with a needle or other probe for delivery of drugs, including siRNAs and vectors.

The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be

reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law (MPEP 2144).

As a whole, the cited references teach the use of siRNA technology for inhibition of genes associated with neurodegenerative disorders. The cited references provide ample guidance teaching one of skill how to stereotactically target and deliver siRNA to specific locations in the brain to reduce gene expression in brain cells affected by diseases such as Alzheimer's and spinocerebellar ataxia. Xia et al. and Driscol teach the design and production of siRNA encoding vectors, and Driscoll suggests at least one potential target gene for treating Alzheimer's disease.

Accordingly, the combined references render the claimed invention prima facie obvious.

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Claims 1, 5, 9, 10, 14, 19, 24, 25, 85–87, and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al. (2002) *Nature* 20:1006–1010; Driscoll et al. (WO 01/49844); Paxinos et al. (2001) *The Mouse Brain in Stereotaxic Coordinates.* Academic Press, 2nd Ed; Cahill et al.; Serra et al. (1996) *Medical Image Analysis* 1(4):317-329; Morel et al. (1997) *J. Comparative Neurology* 387:588-630; Clark et al. (1997) *J. Neuroscience* 17:7385-7395; and Salehi et al. (1999) *J. Neural Transm.* 106:955-986, as applied to claims 1, 9, 10, 14, and 24, above, and further in view of Whitesell et al. (1993) *Proc. Natl. Acad. Sci.* 90:4665-4669; Davidson et al. (US Patent Application Publication 2004/0023390); Matilla et al. (1998) *J. Neuroscience* 18:5508-5516; and Exhibit A: NCBI published mRNA sequence of SCA1 (Mar. 24, 1999).

Xia et al.; Driscoll et al. Paxinos et al.; Cahill et al.; Serra et al. Morel et al. Clark et al., and Salehi et al. are relied on for the reasons given above. These references do not specifically teach the use of an infusion pump or siRNA complementary to an mRNA transcript from the SCA1 gene.

Whitesell et al. teach a system for intraventricular administration of radioactively or fluorescently labeled antisense oligonucleotides into rats. (pages 4665-6). The rat subjects are described as containing 22-guage steel cannulae stereotactically implanted in the lateral ventricle (page 4666). The cannulae serve as ports, and for purposes of this examination, are considered to also represent catheters, through which labeled antisense oligos were injected by bolus injection with a Hamilton syringe or continuous injection using a miniosmotic pump (page 4666). ("Catheter" is defined by Merriam-Webster OnLine as a tubular medical device for insertion into body cavities to permit injection of fluids.) Whitesell et al. report that their study supports the feasibility of continuously perfusing the CNS with therapeutic concentrations of intact antisense oligos, and the possibility of using such therapeutics to target leptomeninigeal and intraparenchymal disease processes (page 4669).

Davidson et al. teach a method for preparing viral vectors encoding small interfering RNA for use in gene silencing therapy of genes associated with neurodegenerative disorders, including spinocerebellar ataxia type 1 (SCA1) (see esp. paragraphs 180-185). The authors contemplate the use of their invention as a method for reducing the expression of a gene product (paragraph 5) such as that associated with SCA (see claims 23 and 48). Thus, Davidson teach the construction of siRNA expression cassettes (paragr. 136-156) and siRNA-encoding recombinant

viruses (paragr 157-170) for general use *in vivo* via direct delivery to a mouse brain (paragr. 209).

Banfi et al. teach the gene sequence of SCA1, encoding ataxin-1, which is said to be responsible for spinocerebellar ataxia. Banfi et al. disclose the full-length mRNA sequence of ataxin-1 mRNA at GenBank Accession No. NM_000332, available to the public 3/24/1999 (see Exhibit A: NCBI online printout of SCA1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to develop siRNA encoding vectors, as taught by Xia et al. and Driscoll et al. for direct intracranial delivery into the brains of mice and humans to reduce the expression of dominant disease-causing genes such as mutant ataxin-1 to inhibit neurodegeneration associated with spinocerebellar ataxia type 1, as taught by Davidson et al. One of skill in the art would have been appraised of the correlation of ataxin-1 protein and SCA1 based on the teachings of Matilla et al. and Banfi et al. who teach that ataxin-1 and isoforms thereof are responsible for the physiological abnormalities associated with SCA1.

One would have been motivated to create such systems for delivering SCA1-targeting small interfering RNA into the brains of mice or rats because Matilla et al. teach that SCA1 has a genetic basis involving the expression of a mutant or toxic form of the SCA1 gene in Purkinje cells of the brain causing loss of these cells and an ataxic phenotype (page 5508).

One would have a reasonable expectation of success given that the combined teachings of Xia et al. Driscoll et al., and Whitesell et al. teach that systems for direct delivery of antisense RNA or vectors encoding siRNA (e.g. short hairpin RNA) can be used effectively to reduce gene expression in brain tissues and that the direct delivery with continuous infusion can result in

potentially therapeutic levels and extensive brain uptake of antisense oligos (see Whitesell throughout), circumventing the obstacles observed with systemic administration through the blood stream. Furthermore, Davidson et al., encourage and teach the use of recombinant siRNA-encoding vectors to treat spinocerebellar ataxia type 1 (SCA1).

Thus in the absence of evidence to the contrary, the invention as a whole as claimed in the instant claims would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Arguments considered:

Applicants argue each of the applied references separately, asserting that each reference on its own fails to reasonably suggest or enable the claimed invention with all of its limitations.

The Examiner agrees that each reference on its own fails to teach the claimed invention with all of its limitations. However, the cited references are not relied on individually but as a whole for what they taught or fairly suggested to one of skill in the art at the time the invention was made.

As a whole, the combined teachings of the instantly cited references are considered to render the invention prima facie obvious in that they teach and/or suggest inhibiting SCA1 expression by direct delivery into the brain of patients afflicted with spinocerebellar ataxia type 1. The combined teachings provide amply guidance, motivation, and a reasonable expectation of success in the field to which they apply for delivering therapeutic nucleic acids, siRNAs and/or vectors thereof to particular regions in the brain, using needles and/or catheters to deliver nucleic acids such antisense DNA, and siRNA into the target region by continuous infusion or bolus delivery. It would have been obvious to one of skill that the Whitesell et al. methods are equally

adapted to siRNAs given that Xia et al. demonstrate that double stranded nucleic acid delivery to brain cells is feasible and will result in uptake and gene expression inhibition of endogenously or episomally expressed genes.

Prior Art not relied upon

The following prior art is not relied upon, but is considered pertinent to applicant's disclosure.

- Elsberry (WO 97/40874), who teaches a system for treating neurodegenerative disorders by brain infusion.
- Elsberry et al. (US Patent 5,735,814) and Elsberry et al. (US Patent 5,814,014), who teaches devices for treating neurodegenerative disorders by brain infusion. On page 27 of the instant application, Applicant states that these devices can be used to deliver small interfering RNA in accordance with the present invention.
- McSwiggen (US Patent Application Publication 2003/0190635), who teaches the preparation and use of small interfering RNA against beta secretase (BACE) to treat Alzheimer's disease.
- Powell et al. (US Patent 6,870,030), who teach antisense oligonucleotides for reducing the expression of aspartyl protease 2 (Asp2) for treatment of Alzheimer's disease.
-

Response to Applicants' Arguments

Applicants' arguments presented on 3/6/06 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Conclusion

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571)272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Louis Wollenberger
Examiner, Art Unit 1635
August 1, 2006

RICHARD SCHNIZER, PH.D.
PRIMARY EXAMINER

1: NM_000332. Reports ...[gi:4506792] The record has been replaced by 51479157

Comment Features Sequence

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  AUTHORS   Banfi,S., Servadio,A., Chung,M.Y., Kwiatkowski,T.J. Jr.,
            McCall,A.E., Duvick,L.A., Shen,Y., Roth,E.J., Orr,H.T. and
            Zoghbi,H.Y.
  TITLE     Identification and characterization of the gene causing type 1
            spinocerebellar ataxia
  JOURNAL   Nat. Genet. 7 (4), 513-520 (1994)
  MEDLINE   95038838
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  AUTHORS   Banfi,S.
  TITLE     Direct Submission
  JOURNAL   Submitted (11-MAY-1994) S. Banfi, Baylor College of Medicine, Dept
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ORIGIN

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